REMARKS

Applicants have studied the Office Action mailed April 6, 2004 and have made amendments to the claims and specification. It is respectfully submitted that the application, as amended, is in condition for allowance. Reconsideration and allowance of the pending claims in view of the above amendments and following remarks is respectfully requested.

Specification/Informalities

The Examiner indicated that the Applicant's amendment to the "Description of the Figure Sheets" section which states "FIGURES A-3FF" needs to be corrected, and the Examiner suggested that the description should instead state "FIGURES 3A-3FF".

To correct the typographical error in the description of Figure 3, Applicants have hereby amended the "Description of the Figure Sheets" section in accordance with the Examiner's suggestion.

Claim Objection:

The Examiner objected to claim 25 in the recitation of "of-SEQ ID NO:1" and suggested that Applicants amend the claim to remove the hyphen between "of" and "SEQ ID NO:1".

To correct the typographical error in claim 25, Applicants have hereby amended claim 25 in accordance with the Examiner's suggestion.

Rejection of claims 4, 8-9, and 24-37 under 35 USC §101 and 35 USC §112, 1st paragraph

The Examiner maintained the rejection of claims 4, 8-9, and 24-37 as not being supported by either a specific and substantial asserted utility or a well-established utility and, consequently, one skilled in the art would not know how to use the claimed invention.

In summary, the Examiner asserts that the asserted use of the claimed nucleic acid as a therapeutic target and for treatment and/or diagnosis of developmental disorders is

not substantial as further experimentation is required for such use, at least for the following reasons. First, while the claimed polynucleotides encode polypeptides that share sequence identity with nephronectins from mice, there is no indication in the specification that the claimed nucleic acids encode biologically active polypeptides. Thus, it is just as likely that the polypeptides encoded by the claimed polynucleotides are biologically inactive. Thus, further experimentation would be required to determine whether the encoded polypeptides are biologically active and have the ability to interact with $\alpha 8\beta 1$. The Examiner also states that neither the specification nor the prior art evidence provides guidance as to the biological significance of the interaction of nephronectin with $\alpha 8\beta 1$, and that such guidance is necessary in order for one to use the claimed polynucleotide as a therapeutic/and or diagnostic agent. The Examiner further states that there is no indication in the specification or the prior art that the claimed polynucleotide can be used for therapeutic or diagnostic purposes and neither the specification nor the prior art provides the necessary guidance for using the claimed polynucleotide for such purposes. The Examiner concludes that, consequently, the asserted utilities for the claimed polynucleotide for treatment and/or diagnosis of developmental disorders are not specific and substantial.

In response, Applicants respectfully assert that novel nephronectins like the nephronectin encoded by the claimed polynucleotides are supported by specific and substantial utilities related to the treatment (and/or diagnosis) of developmental disorders, as indicated on page 3 of the specification. This has been established in the art, such as by Brandenberger *et al.* (*J Cell Biol* 2001 Jul 23;154(2):447-58), which was discussed in Applicant's response filed March 3, 2004.

In further support of Applicant's position, and the disclosure of Brandenberger *et al.*, is the reference of Morimura *et al.*, "Molecular cloning of POEM: a novel adhesion molecule that interacts with alpha8beta1 integrin", *J Biol Chem.* 2001 Nov 9;276(45):42172-81 (Epub 2001 Sep 06), which is provided in the IDS submitted herewith.

The protein referred to as "POEM" ("preosteoblast epidermal growth factor-like repeat protein with meprin, A5 protein, and receptor protein-tyrosine phosphatase μ

domain") by Morimura *et al.* is identical to the protein referred to by Brandenberger *et al.* as "nephronectin". This is stated on page 42181 (last paragraph of 1st column) of Morimura *et al.* as follows: "After this manuscript was submitted, Brandenberger *et al.* also reported detailed characterization of a novel $\alpha 8\beta 1$ integrin ligand named nephronectin. The amino acid sequence of nephronectin was completely identical with that of POEM." Morimura *et al.* also characterize POEM as a novel ligand molecule for $\alpha 8\beta 1$ integrin.

Regarding POEM (i.e., nephronectin), Morimura *et al.* state the following:

- "These results suggest that POEM is a novel ligand for $\alpha 8\beta 1$ integrin and that POEM may be involved in the development and function of various tissues, such as kidney, bone, muscles, and endocrine organs." (p. 42172, last sentence of abstract)
- Regarding integrins, "Integrins are involved in tissue repair, development, and immune responses. Integrins also serve important functions in bone development and remodeling. Recently, it was reported that $\beta 1$ integrin was significantly involved in osteoblastic function. Expression of dominant negative $\beta 1$ subunit in osteoblasts significantly reduced the bone-forming activity of osteoblasts. Matrix proteins produced by osteoblastic cells are the major target molecules not only for osteoblasts themselves but also for osteoclastic cells. Therefore, identification of a novel adhesion molecule produced by osteoblastic cells provides a new insight into the biology and development of bone tissue." (p. 42172, 2nd paragraph of 2nd column). POEM is reported by Morimura *et al.* as a novel adhesion protein.
- "In the developing mouse embryo, POEM was expressed in the endocrine organs (parathyroid gland, thyroid gland, hypophysis, and pineal organ). These endocrine organs are closely related to growth, bone metabolism, and calcium and phosphorus homeostasis. In the mouse embryo, POEM mRNA showed a unique distribution in and around the developing bone, in the tooth germ, and in muscle. These data also suggest the relationship between POEM and calcium metabolism. Osteoblastic cells produce a number of ECM (extracellular matrix) proteins. For

example, type I collagen and osteopontin are up-regulated after osteoblast maturation. On the other hand, we noted that the expression of POEM was down-regulated as osteoblastic cell differentiation proceeded. The distribution of POEM expression in the mouse embryo also suggested the role of POEM in the early stage of osteoblastic cell differentiation. POEM has an RGD (Arg-Gly-Asp) cell adhesion motif, which is known to interact with integrins. In this study, we found POEM to be a novel candidate ligand molecule for $\alpha 8\beta 1$ integrin. In osteoclasts, integrins have been shown to play important functional roles by regulating cell attachment and bone resorbing activity. POEM was preferably expressed in preosteoblastic cells, which do not seem to interact with directly osteoclastic cells; however, integrins have been shown to play significant roles not only in osteoclasts but also in osteoblasts. Mice deficient in the $\beta 1$ integrin subunit showed significantly less bone-forming activity. Moursi *et al.* also reported that integrins, such as $\alpha 5\beta 1$, $\alpha 8\beta 1$, $\alpha 3\beta 1$, and $\alpha 4\beta 1$ are critical for mineralized nodule formation and osteoblast differentiation. Therefore, POEM may play important roles in osteoblastic function by sending survival signals via $\alpha 8\beta 1$ integrin and mediating cell-cell interaction." (paragraph that spans pp. 42180-42181).

Thus, it is clear from both Morimura *et al.* and Brandenberger *et al.* (which was discussed in Applicant's response filed March 3, 2004) that the utility of nephronectins (which may also be referred to as POEM proteins) is well established in the art because, for example, nephronectins have been characterized as playing important roles in specific aspects of development. Therefore the skilled artisan will recognize that the claimed invention has specific and substantial utilities related to the treatment/diagnosis of developmental disorders. Consequently, because the claimed invention is supported by patentable utilities, Applicants respectfully request that the Examiner reconsider and withdraw the rejections under 35 USC §101 and 35 USC §112, 1st paragraph.

Conclusions

By way of the above amendments, claim 25 has been amended. As such, claims 4, 8-9, and 24-37 remain pending. The amendments to the claims and specification add no new subject matter and their entry is respectfully requested.

In view of the above amendments and remarks, Applicants respectfully submit that the application and claims are in condition for allowance, and request that the Examiner reconsider and withdraw the rejections and objections. If for any reason the Examiner finds the application other than in condition for allowance, the Examiner is invited to call the undersigned agent at (240) 453-3812 should the Examiner believe a telephone interview would advance prosecution of the application.

Respectfully submitted,

CELERA GENOMICS

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